PATENT COOPERATION T EATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/013319	03.12.2008	03.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/575 A61P19/08 A61P19/02 A61P19/10 A61P9/10 A61P3/04 A61P17/14

Applicant
PARHAMI, FARHAD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Written Opinion
2 MONTH REMINDER 5/8/09
1 MONTH REMINDER 6/8/09
2 WEEK REMINDER 6/24/09
3 DAY REMINDER 7/5/09
ACTION DUE AND DATE 7/8/09
SZP

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich	see form PCT/ISA/210	Madalinska, K

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/013319

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-40
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Reference is made to the following documents:

   D1: WO 2007/098281 A;
   D2: WO 2007/028101 A;
   D3: WO 2005/020928 A;
   D4: *Journal of Bone and Mineral Research* **2005**, *20*, S361 - XP009114658;
   D5: WO 2008/115469.

2. The relevant passages are those indicated in the search report, unless otherwise specified.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. The patentability of claims 1-40 is *inter alia* dependent upon their formulation as well as upon national and regional laws and no criteria is provided in this field by the PCT. Their assessment will be carried out based on the alleged effects of the compounds of formula (I) searched in the International Search Report.

4. None of the documents in the prior art discloses the compound of formula (I) for use in the treatment of bone disorder, osteoporosis, osteoporitis, osteoarthritis, a bone fracture, obesity, xanthoma, cardiovascular disorder, arteriosclerosis, myocardial infarction, peripheral vascular disease, stroke and/or alopecia.

   D1 discloses the treatment of bone and vascular disorders or alopecia by using a compound of formula (I), which are excluded by means of disclaimer from the claimed subject-matter.
   D2-D4 disclose treatment of bone disorders by using oxysterols including 20-hydroxycholesterol, that is excluded by means of disclaimer from the claimed subject-matter.

   Accordingly, D1-D4 are not prejudicial to novelty of the claimed subject-matter and therefore, claims 1-40 are considered as meeting the requirements of Article 33(2) PCT.

5. However, the Applicant should bear in mind the content of D5 (cited under section VI) which could be held prejudicial to the novelty of claims 1-6, 10, 13-25, 28-40 during Regional or National examination phase(s).

6. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-40 does not involve an inventive step in the sense of Article 33(3) PCT.

D1 relating to the oxysterols of formula (I) as the inhibitors of Hedgehog pathway for use in the treatment of bone and vascular disorders or alopecia is considered as the closest prior art for the subject-matter of claims 1-40.

D2-D4 relating the treatment of bone disorders such as osteoporosis by using 17-substituted oxysterols including 20-hydroxycholesterol can also be regarded as the closest prior art for the subject-matter of claims 1-9 and 12-40.

The compounds of D1-D4 which are excluded by the proviso of claims 1 and 21 appear to be only, if any, minor modifications of the claimed derivatives.

Therefore, such a minor modification must be regarded as obvious solution to the provision of alternative compounds for the treatment of the bone and vascular disease or alopecia of the present application.

Accordingly, an inventive step cannot be acknowledged in the absence of evidence showing that substantially all the claimed compounds have unexpected property or improved activity with respect to the structurally closest prior art compounds of D1-D4.

Re Item VI

Certain documents cited

7. D5 is cited under Rules 64.3 and 70.10 PCT.

Re Item VIII

Certain observations on the international application

8. The present independent claims 1, 13 and 21 encompass a composition/compound defined by their desired function ("...wherein the compounds induces a biological response...", "...an amount sufficient to induce..."), contrary to the requirements of clarity of Article 6 PCT. The claims attempt to define the subject-matter in terms of the result to be achieved without providing the technical features necessary for achieving this result. Such a "result-to-be-achieved" type definition does not allow the scope of the claim to be ascertained.

   The subject-matter for which protection is desired should be defined in concrete terms, i.e. in terms of how the aforementioned result is to be achieved and in terms clearly defining the instructions enabling the person skilled in the art to reproduce in practice the invention without undue burden and without inventive skills.

9. Independent claim 14 does not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating a hedgehog pathway response, a Wnet inhibitory Factor-1 pathway), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

10. The number of independent claims is unreasonable (Rule 6.1(a) PCT).

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003